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(12) (19) (CA) **Brevet-Patent**

(11) (21) (C) **2,114,156**
(22) 1994/01/25
(43) 1994/07/27
(45) 2001/01/02

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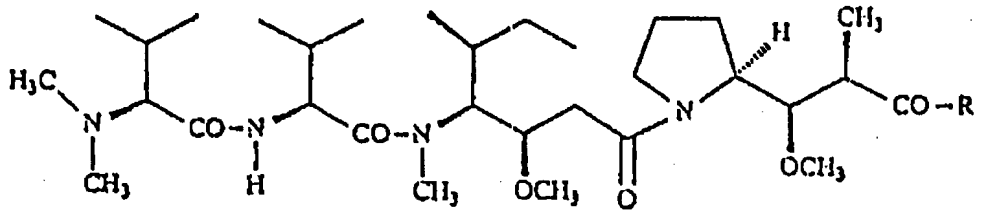
(73) Arizona Board of Regents, US

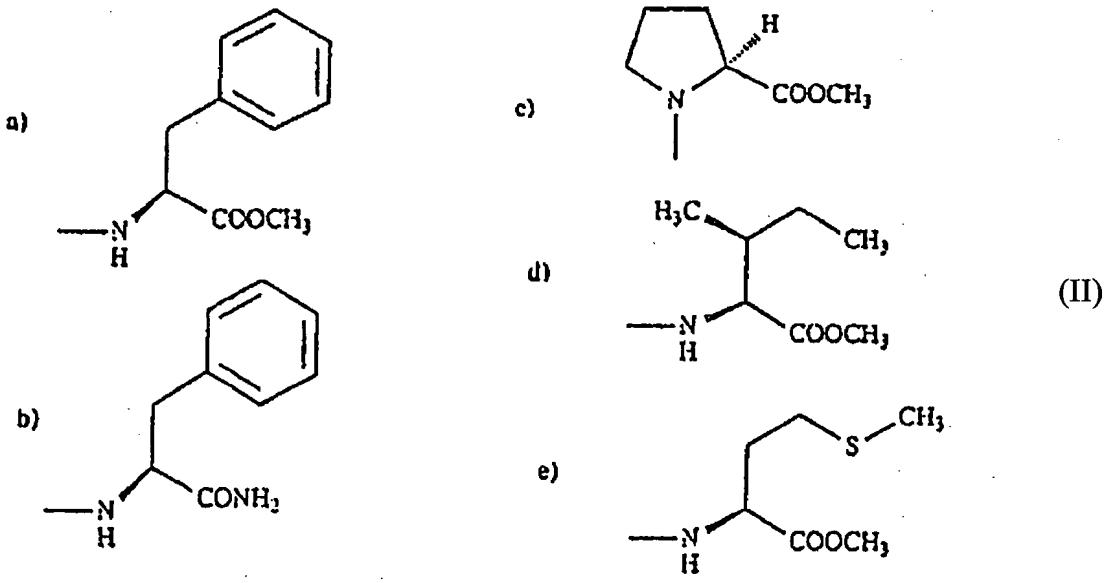
(51) Int.Cl.[6] C07K 7/02, A61K 38/08, C07K 1/02
(30) 1993/01/26 (009,296) US

(54) **CARACTERISATION ET SYNTHESE DE PENTAPEPTIDES SELECTIONNES**

(54) **ELUCIDATION AND SYNTHESIS OF SELECTED PENTAPEPTIDES**




(I)



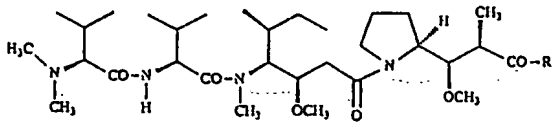

(II)

(57) The sea hare Dolabella auricularia has yielded many structurally distinct peptides which possess antineoplastic activity. Presently the compound denominated "dolastatin 10" represents then most important of such peptides because of its demonstrated potential as an anticancer drug. The present invention relates to the systematic creation of five unique pentapeptides by selectively coupling a tripeptide - trifluoroacetate salt with a preselected dipeptide-trifluoroacetate salt which provide active molecules capable of emulating the measured therapeutic effect of dolastatin 10. The pentapeptides hereof have the structure shown below: (see formula I) wherein R is selected from the following group of substituents: (see formula II).

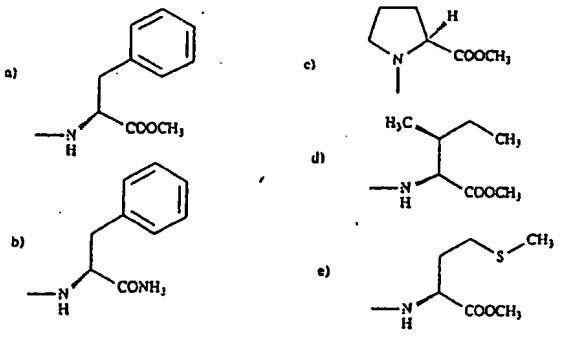
ABSTRACT OF THE DISCLOSURE

The sea hare Dolabella auricularia has yielded many structurally distinct peptides which possess antineoplastic activity. Presently the compound denominated "dolastatin 10" represents the most important of such peptides because of its demonstrated potential as an anticancer drug.

The present invention relates to the systematic creation of five unique pentapeptides by selectively coupling a tripeptide - trifluoro-acetate salt with a preselected dipeptide-trifluoroacetate salt which provide active molecules capable of emulating the measured therapeutic effect of dolastatin 10. The pentapeptides hereof have the structure shown below:



wherein R is selected from the following group of substituents:



# ELUCIDATION AND SYNTHESIS OF SELECTED PENTAPEPTIDES

## INTRODUCTION

This invention relates generally to the field of anti-neoplastic compounds, and more particularly to the elucidation and synthesis of selected pentapeptides prepared by coupling dipeptide salts with the known tripeptide-trifluoroacetate salt. More particularly, the present invention relates to the synthesis of five pentapeptides by the coupling of a tripeptide-trifluoroacetate salt with the respective dipeptide-trifluoroacetate salt, which was itself prepared by the coupling of dolaproine with the respective amino acid. This coupling results in compounds which are found to exhibit effective antineoplastic activity against various human cancerous tumor cell lines.

## BACKGROUND OF THE INVENTION

Ancient marine invertebrate species of the Phyla Bryozoa, Molluska, and Porifera have been well established in the oceans for over one billion years. Such organisms have undergone trillions of biosynthetic reactions in their evolutionary chemistry to reach their present level of cellular organization, regulation and defense.

For example, marine sponges have changed minimally in physical appearance for nearly 500 million years. This suggests a very effective chemical resistance to evolution in response to changing environmental conditions over that period of time. Recognition of the potential for utilizing this biologically potent marine animal for medicinal purposes was recorded in Egypt about 2,700 BC and by 200 BC sea hare extracts were being used in Greece for their curative affect. This consideration along with the observation that

marine animals, e.g. invertebrates and sharks, rarely develop cancer led to the systematic investigation of marine animal and plant anticancer compounds.

By 1968 ample evidence had been obtained, based on the U.S. National Cancer Institute's (NCI) key experimental cancer study systems, that certain marine organisms could provide new and antineoplastic and/or cytotoxic agents and might also lead to compounds which would be effective in the control and/or eradication of viral diseases.

Further, these marine organisms were believed to possess potentially useful drug candidates of unprecedented structure which had eluded discovery by other methods of medicinal chemistry. Fortunately, these expectations have been realized, e.g. the discovery of the bryostatins, dolastatins and cephalostatins, many of which are now in preclinical development or human clinical studies.

Those researchers presently involved in medicinal chemistry know well the time lag between the isolation of a new compound and its introduction to the market. Often this procedure takes several years and may take decades. As a result, industry, in association with the U.S. Government, has developed a system of testing criteria which serves two purposes. One is to eliminate those substances which are shown through testing to be economically counterproductive. The second, more important purpose serves to identify those compounds which demonstrate a high likelihood of success and therefore warrant the further study and qualification, and attendant expense, necessary to meet the stringent regulatory requirements which control the ultimate market place.

The current cost to develop the necessary data approaches ten million dollars per compound. As

such, economics dictate that such a huge investment will be made only when there is a reasonable opportunity for it to be recovered. Absent such opportunity, there will be no investment and the research involving the discovery of these potentially life saving compounds will cease. Only two hundred years ago many diseases ravaged mankind. Many of these now have been controlled or eradicated. During the advancement of means to treat or eliminate these diseases, work with appropriate animals was of critical importance.

Current research in the control of cancer in the United States is coordinated by the National Cancer Institute (NCI). To determine whether a substance has anti-cancer properties, the NCI has established a systematic protocol. This protocol, which involves the testing of a substance against a standard cell line panel containing 60 human tumor cell lines, has been verified and has been accepted in scientific circles. The protocol, and the established statistical means for analyzing the results obtained by the standardized testing are fully described in the literature. See: Boyd, Dr. Michael R., Principles & Practice of Oncology, PPO Updates, Volume 3, Number 10, October 1989, for an in depth description of the testing protocol; and Paull, K. D., "Display and Analysis of Patterns of Differential Activity of Drugs Against Human Tumor Cell Lines; Development of Mean Graph and COMPARE Algorithm", Journal of the National Cancer Institute Reports, Vol. 81, No. 14, Page 1088, July 14, 1989 for a description of the methods of statistical analysis.

Numerous substances have been discovered which demonstrate significant antineoplastic or tumor inhibiting characteristics. As stated above, many of these compounds have been extracted, albeit with great difficulty, from marine animals such as the

sponge and sea hare. Once isolation and testing of these compounds has been accomplished, a practical question remains, namely how to produce commercially significant quantities of the desired substance.

Quinine, which is available in practical quantities from the bark of the cinchona plant, differs from the compounds which are extracts of marine creatures possessing antineoplastic qualities. The collection and processing of these later compounds from their natural sources ranges from grossly impractical to the utterly impossible. Ignoring the ecological impact, the population of these creatures and the cost of collection and extraction make the process unworkable. Artificial synthesis of the active compounds is the only possible solution.

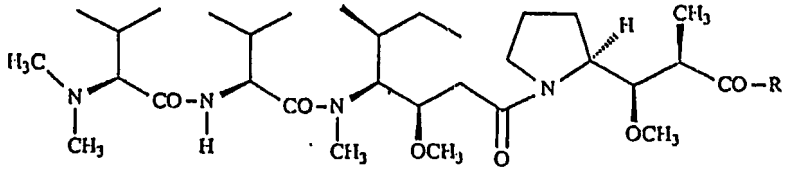
Therefore, the elucidation of the structure of these antineoplastic compounds is essential. After the structure has been determined, then a means of synthesis must be determined. This is often a long and arduous procedure due to the idiosyncratic complexity of these naturally occurring, evolutionary modified compounds. In addition, research is necessary to determine whether any portion of the naturally occurring compound is irrelevant to the desired properties, so that focus can be on the simplest structure having the perceived properties.

## BRIEF SUMMARY OF THE INVENTION

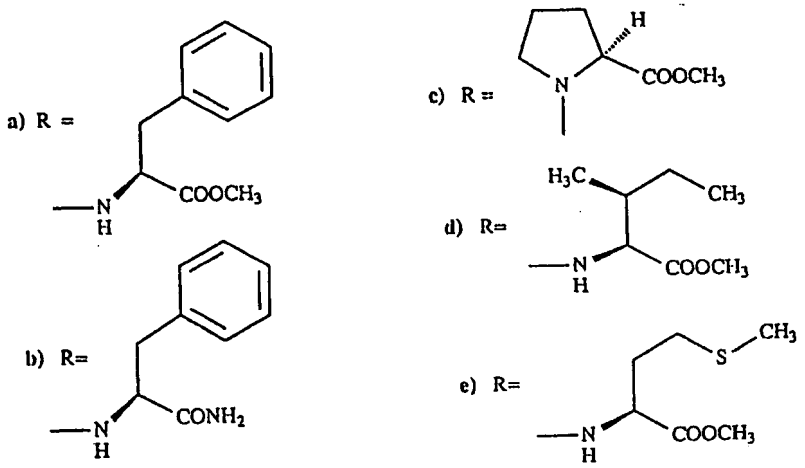
The synthesis of potentially useful peptides presents one of the most essential and promising approaches to new types of anticancer and immunosuppressant drugs. The Dolastatins, an unprecedented series of linear and cyclic antineoplastic and/or cytostatic peptides isolated from Indian Ocean sea hare Dolabella auricularia represent excellent leads for synthetic modification. The very productive sea hare Dolabella auricularia has produced a number of structurally distinct peptides with excellent antineoplastic activity. Presently Dolastatin 10, a linear pentapeptide represents the most important member and is a potentially useful antineoplastic agent. Dolastatin 10 shows one of the best antineoplastic activity profiles against various cancer screens presently known.

This research has led to an effective method

for the synthesis of new and very potent anti-cancer pentapeptides related in structure to Dolastatin 10. The present invention involves the structure and synthesis of five such pentapeptides as shown below.



3(a-e)




Accordingly, the primary object of the subject invention is the synthesis of five pentapeptide derivatives of dolastatin 10 which exhibit effective antineoplastic activity against various human cancerous tumor cell lines.

Another object of the subject invention is the synthesis of pentapeptide derivatives of dolastatin 10 through the coupling of respective tripeptide and dipeptide trifluoroacetate salts, wherein the dipeptide salt was prepared by the coupling of dolaproine and the respective amino acid.

These and still further objects as shall

hereinafter appear are readily fulfilled by the present invention in a remarkably unexpected manner as will be readily discerned from the following detailed description of an exemplary embodiment thereof.

## DESCRIPTION OF THE PREFERRED EMBODIMENT

The synthesis of potentially useful peptides presents one of the most essential and promising approaches to new types of anticancer and immunosuppressant drugs. The Dolastatins, an unprecedented series of linear and cyclic antineoplastic and/or cytostatic peptides isolated from Indian Ocean sea hare Dolabella auricularia represent excellent leads for synthetic modification. The very productive sea hare Dolabella auricularia has produced a number of structurally distinct peptides with excellent antineoplastic activity. Presently Dolastatin 10, a linear pentapeptide represents the most important member and is a potentially useful antineoplastic agent. Dolastatin 10 shows one of the best antineoplastic activity profiles against various cancer screens presently known. Recently the total synthesis and absolute configuration of this structurally unique and biologically active peptide was reported. This compound has been tested in vivo and demonstrated significant activity, as shown below.

Experimental Anticancer Activity of Dolastatin 10 in

Murine in vivo Systems, T/C (μg/kg)

P388 Lymphocytic Leukemia
toxic (13.0)
155 and 17% cures (6.5)
146 and 17% cures (3.25)
137 (1.63)

L1210 Lymphocytic Leukemia
10152 (13)
135 (6.5)
139 (3.25)
120 (1.63)

B16 Melanoma
238 and 40% cures (11.11)
182 (6.67)
205 (4.0)
171 (3.4)
142 (1.44)

20M5076 Ovary Sarcoma
toxic (26)
166 (13)
142 (6.5)
151 (3.25)

LOX Human Melanoma Xenograph
to (Nude Mouse)
toxic (52)
301 and 67% cures (26)
301 and 50% cures (13)
30206 and 33% cures (6.5)
170 and 17% cures (3.25)
LOX in separate experiments
340 and 50% cures (43)
181 and 33% cures (26)
192 (15)
138 and 17% cures (9.0)

Human Mammary Xenograph
Nude Mouse
Toxic (26)
137 (13)
178 (6.25)

OVCAR-3 Human Ovary Xenograph
Nude Mouse
300 (40)

MX-1 Human Mammary Xenograft
(Tumor Regression)
14 (52)
50 (26)
61 (13)
69 (6.25)

Dolastatin 10 has also been tested against a minipanel from the NCI Primary screen. These results appear below, showing the amount of Dolastatin 10 required to attain $GI_{50}$ in μg/ml, against the cell lines set forth below.

| OVCAR-3 (A) | SF 295 (B) | A498 (C) | NCI-H460 (D) |
|---|---|---|---|
| $9.5 \times 10^{-7}$ | $7.6 \times 10^{-8}$ | $2.6 \times 10^{-5}$ | $3.4 \times 10^{-6}$ |

| KM20L2 (E) | SK-MEL-5 |
|---|---|
| $4.7 \times 10^{-6}$ | $7.4 \times 10^{-6}$ |

From the foregoing, it can be seen that the in vitro activity of dolastatin 10 in the primary screen has been confirmed by in vivo animal tests.

For the compounds disclosed in this application, the in vitro tests disclosed above are reasonably accurate predictors of anticancer activity, and not mere indicators of the desirability for further testing.

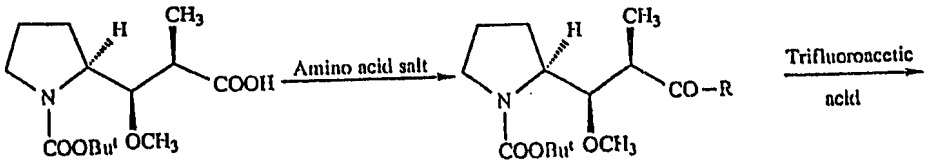
These newly discovered pentapeptide compounds (**3a-3e**), related to Dolastatin 10, are formed by the coupling of the respective dipeptide-fluoroacetate salts (**2a-2e**) with the known tripeptide-trifluoroacetate salt (**4**). The dipeptides (**1a-1e**) were in turn prepared by coupling dolaproine (**5**) with the respective amino acids. All compounds were characterized (physical and spectroscopic data) and tested against the murine lymphocytic P388 leukemia cell line as well as six major human cancer cell lines. The remarkable cancer cell growth inhibitory data are shown in Table 1.

Table 1. Potent Inhibition of Cancer cell lines by pentapeptides 3a-e

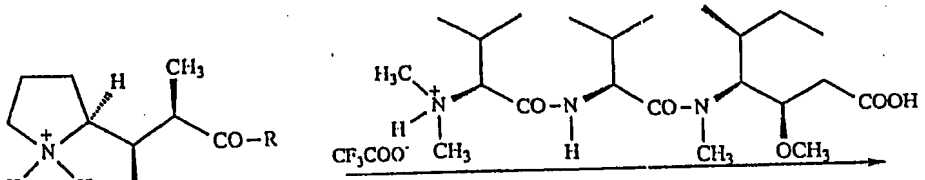
| TEST | CELL TYPE | CELL LINE | PENTAPEPTIDE | | | | |
|---|---|---|---|---|---|---|---|
| μg/ml | | | 3 a | 3 b | 3 c | 3 d | 3 e |
| $ED_{50}$ | MOUSE LEUKEMIA | P388 | 0.0667 | 0.0195 | 0.0088 | 0.000441 | 0.000389 |
| GI-50 | Ovarian | OVCAR-3 | <0.0001 | 0.0076 | <0.0001 | <0.0001 | <0.0001 |
| | CNS | SF-295 | <0.0001 | 0.00085 | <0.0001 | <0.0001 | <0.0001 |
| | Renal | A498 | <0.0001 | 0.00097 | <0.0001 | <0.0001 | <0.0001 |
| | Lung-NSC | NCI-H460 | <0.0001 | 0.000095 | <0.0001 | <0.0001 | <0.0001 |
| | Colon | KM20L2 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| | Melanoma | SK-MEL-3 | <0.0001 | 0.00017 | <0.0001 | <0.0001 | <0.0001 |
| TGI | Ovarian | OVCAR-3 | 0.0011 | 0.0037 | <0.0001 | <0.0001 | <0.0001 |
| | CNS | SF-295 | 0.00017 | 0.049 | 0.0024 | 0.17 | 0.056 |
| | Renal | A498 | 0.0029 | 0.0062 | 0.0054 | <0.0001 | >1 |
| | Lung-NSC | NCI-H460 | 0.011 | 0.011 | 0.0013 | 0.00088 | 0.13 |
| | Colon | KM20L2 | 0.0011 | 0.019 | 0.0022 | <0.0001 | 0.00015 |
| | Melanoma | SK-MEL-3 | 0.00068 | 0.012 | <0.0001 | <0.0001 | >1 |
| LC-50 | Ovarian | OVCAR-3 | >1 | 0.066 | >1 | 0.043 | >1 |
| | CNS | SF-295 | >1 | >1 | >1 | >1 | >1 |
| | Renal | A498 | >1 | >1 | >1 | >1 | >1 |
| | Lung-NSC | NCI-H460 | >1 | >1 | >1 | >1 | >1 |
| | Colon | KM20L2 | >1 | 0.083 | >1 | >1 | >1 |
| | Melanoma | SK-MEL-3 | >1 | >1 | >1 | >1 | >1 |

The human cancer cell lines results shown for pentapeptides **3a-e** in Table I illustrate remarkably patent and selective activity against human ovary, CNS (brain), kidney, lung, colon and melanoma type cancers. In this respect, each compound parrots a pattern previously discovered for Dolastatin 10 and as such is reasonably expected to generate in vivo data results comparable to those reported above for Dolastatin 10.

The scheme and structures of these pentapeptides appear below:




5 1(a-e)



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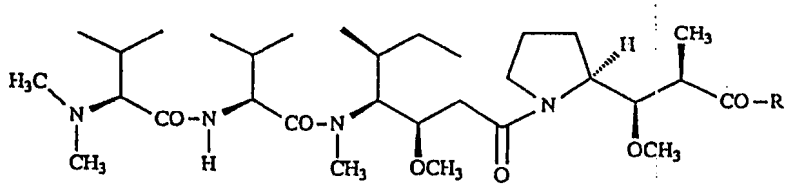

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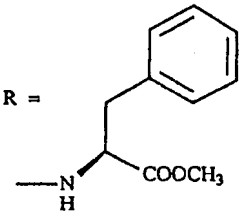
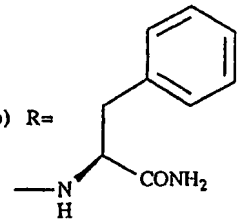
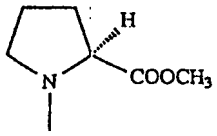
a) R =



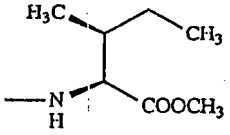
b) R=



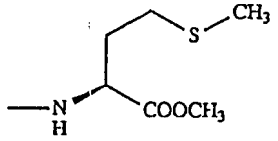
c) R =



d) R=



e) R=



SCHEME 1

**General Procedure for the Synthesis of Dipeptides (1a-1e):**

To a solution of dolaproine tfa salt (1mmol) and the amino acid salt (1mmol) in dry dichloromethane (2ml), cooled to ice-bath temperature under an argon atmosphere was added dry triethylamine (3mmol) followed by diethylcyanophophonate (1.1mmol). The solution was stirred at the same ice bath temperature for 1-2 hr. The salts that precipitated were collected, the solvent was evaporated (under reduced pressure) and the residue chromatographed over a SILICA GEL column with solvents noted to obtain the respective dipeptides.

**i) Boc-Dap-Phe-$OCH_3$ (1a):**

Chromatographic separation on a SILICA GEL column with 3:1 hexane-acetone as the eluent resulted in the required dipeptide as a thick oil. Crystallization from ether-hexane gave sparkling crystals of the pure compound (**1a**, 96%); m.p. = 125°C; $[\alpha]_D^{25}$ = -15.1° (c 0.41, $CHCl_3$); IR(thin film): 3314, 2974, 2934, 2878, 1748, 1692, 1663, 1537, 1456, 1400, 1366, 1173, 1101 and 700; $^1H$ NMR (300MHz, $CDCl_3$): 1.163(d, J=7.0Hz, 3H, $CH_3$), 1.4816(s, 9H, t-Bu), 1.624-1.850(m, 4H, 2 x $CH_2$), 2.25-2.45(m, 1H, CHCO), 3.045(dd, J=13.9 and 7.8Hz, 1H, 1/2 $CH_2$-Ph), 3.175(dd, J=13.8 and 5.55Hz, 1H, 1/2 $CH_2$-Ph), 3.3642(s, 3H, $OCH_3$), 3.3701(s, 3H, $OCH_3$), 3.50-3.60(m, 1H, CH-$OCH_3$), 3.7422(m, 2H, $CH_2$-N), 3.85(m, 1H, pro CH-N), 4.80(m, 1H, phe CH-N), 6.10, 6.75(m, 1H, NH) and 7.10-7.32(m, 5H, Ph); MS: m/z 416[M-$CH_3OH$], 375, 316, 264, 210, 170, 114(100%) and 70. Anal. Found: H: 8.12, N: 6.20. $C_{24}H_{36}N_2O_6$ requires H: 8.09, N: 6.25.

**ii) Boc-Dap-Phe-$NH_2$ (1b):**

Chromatographic purification using a SILICA GEL column with 1:1 hexane-acetone as the eluent

gave the required dipeptide as a crystalline solid. Recrystallization from acetone gave sparkling crystals of the pure compound (**1b**, 65% ); m.p. = 199-200°C (acetone); $[\alpha]_D^{25}$ = -40° (c 0.15, $CHCl_3$); IR(thin film): 3302, 3198, 2974, 2934, 2878, 1669, 1539, 1456, 1404, 1366, 1169, 1111 and 700; $^1H$ NMR (300MHz, $CDCl_3$): 1.019(brs, 3H, $CH_3$), 1.426(s, 9H, t-Bu), 1.55-1.90(m, 4H, 2 x $CH_2$), 2.30(quintet, 1H, CH-CO), 3.00-3.25(m, 3H, $CH_2$-N, CH-$OCH_3$), 3.349(s, 3H, $OCH_3$), 3.60-3.75(m, 1H, pro CH-N), 4.60-4.80(m, 1H, phe CH-N), 5.30(brs, 1H, NH), 6.267(d, J=7.2Hz, 1H, NH), 6.90(brm, 1H, NH) and 7.164-7.306(m, 5H, $C_6H_5$); MS: m/z 433($M^+$), 401(M-MeOH), 360, 301, 247, 232, 210, 170, 154, 138, 114 and 70(100%). Anal. Found: C: 63.75, H:8.18, N:9.62. $C_{23}H_{35}N_3O_5$ requires C: 63.72, H: 8.14, N: 9.69.

**iii) Boc-Dap-Pro-$OCH_3$ (1c):**

Chromatographic separation on a SILICA GEL column with 3:2 hexane-acetone as the eluent gave the required dipeptide as a thick oil (**1c**, 92% ); $[\alpha]_D^{25}$ = -101.5° (c 0.2, $CHCl_3$); IR(neat): 2974, 2880, 1748, 1692, 1647, 1398, 1366, 1171and 1098; $^1H$ NMR (300MHz, $CDCl_3$): 1.222(d, J=7.0Hz, 3H, $CH_3$), 1.440(s, 9H, t-Bu), 1.65-2.20(m, 8H, 4 x $CH_2$), 2.60-2.70(m, 1H, CH-CO), 3.10-3.22(m, 1H, CH-$OCH_3$), 3.417(s, 3H, $CH_3$), 3.45-3.65(m, 4H, 2 x $CH_2$-N), 3.675(s, 3H, $OCH_3$), 3.74-3.83(m, 1H, CH-N) and 4.447(dd, J=8.55 and 3.5Hz, 1H, CH-$COOCH_3$). HRFABMS: m/z 399.24880$[M+H]^+$. $C_{20}H_{35}N_2O_6$ requires 399.24951.

**iv) Boc-Dap-Ile-$OCH_3$ (1d):**

Chromatographic purification on a SILICA GEL column with 3:2 hexane-ethyl acetate as the eluent yielded the required dipeptide as an oily liquid ( **1d**, 72%); m.p. = 76-77°C (acetone); $[\alpha]_D^{25}$ = -28.2° (c 0.17, $CHCl_3$); IR(thin film): 3325, 2971, 2936, 2878, 1746, 1694, 1667, 1530, 1478, 1398, 1254, 1175, 1105, 868 and 774; $^1H$ NMR (300MHz, $CDCl_3$):

0.882(d, J=6.9Hz, 3H, $\underline{CH_3}$-CH), 0.9012(t, J=7.4Hz, 3H, $\underline{CH_3}$-$CH_2$), 1.05-1.24(m, 5H, $CH_3$, $\underline{CH_2}$-$CH_3$), 1.4526(s, 9H, t-Bu), 1.65-2.00(m, 5H, 2 x $CH_2$, $\underline{CH}$-$CH_2$), 2.30-2.50(m, 1H, CH-CO), 3.18-3.28(m, 1H, $\underline{CH}$-$OCH_3$), 3.422(s, 3H, $OCH_3$), 3.48-3.60(m, 1H, pro $\underline{CH}$-N), 3.699(s, 3H, $OCH_3$), 3.72-3.82(m, 1H, 1/2 $CH_2$-N), 3.88-3.98(m, 1H, 1/2 $CH_2$-N), 4.44-4.58(m, 1H, ile CH-N) and 6.15, 6.7(m, 1H, NH); MS: m/z 382(M-MeOH), 341, 282, 245, 230, 210, 170, 114, 70(100%) and 57. Anal. Found: C: 61.06, H: 9.25, N: 6.64. $C_{21}H_{38}N_2O_6$ requires C: 60.84, H: 9.24, N: 6.76.

**v) Boc-Dap-Met-$OCH_3$ (1e):**

Chromatographic separation on a SILICA GEL column using 3:2 hexane-acetone as the eluent gave the required dipeptide as a solid (1e, 83%); m.p. = 68-70°C; $[\alpha]_D^{25}$ = -27.6° (c, 0.59, $CHCl_3$); IR(neat): 3312, 2974, 2934, 2878, 1748, 1692, 1663, 1539, 1398, 1366, 1256, 1171, 1115, 866 and 774; $^1H$ NMR ($CDCl_3$): 1.223(brs, 3H, CH-$CH_3$), 1.441(brs, 9H, t-Bu), 1.6-1.2(m, 6H, 3x$CH_2$), 2.070 (s, 3H, S-$CH_3$), 2.3-2.55(m, 3H, $CH_2$-S, CH-CO), 3.15-3.35 (m, 2H, N-$CH_2$), 3.420 (s, 3H, $OCH_3$), 3.55(m, 1H, CH-$OCH_3$), 3.716(brs, 3H, $COOCH_3$), 3.85-4.0(m, 1H, pro CH-N), 4.6(brm, 1H, met CH-N), 6.3(brm, 1H, NH); MS (m/z): 432 ($M^+$), 400, 359, 258, 210, 170, 114(100%). Anal. Found: C: 55.35, H: 8.33, N: 6.53, S: 7.23. $C_{20}H_{36}N_2O_6S$ requires C: 55.53, H: 8.39, N: 6.48, S: 7.41.

**Synthesis of phenylalanine amide trifluoroacetate salt:**

To a solution of t-boc-phenylalanine amide (3, 80mg, 0.303mmol) in dichloromethane (0.5ml) was added trifluoroacetic acid (1ml) at ice-bath temperature and the solution was stirred at the same temperature for 1.5 hr. under argon atmosphere. The solvents were removed under reduced pressure and the residue taken into toluene and toluene also removed under reduced pressure to obtain a white solid of the trifluoroacetate salt

(80mg, 95%); $^1$H NMR (DMSO-$d_6$, 300MHz): 2.95-3.10(m, 2H, $C_6H_5$-$CH_2$), 3.3209(brs, 2H, $NH_2$), 3.9408(brs, 1H, CH-N), 7.236-7.317(m, 5H, $C_6H_5$) and 7.528, 7.862, 8.150(brs, 3H, $NH_3^+$).

**DEPROTECTION OF DIPEPTIDES 1a-e WITH TRIFLUOROACETIC ACID- GENERAL PROCEDURE:**

To a solution of the Boc-protected dipeptide (1mmol) in dry dichloromethane (2ml, cooled to ice-bath temperature, under an argon atmosphere) was added trifluoroacetic acid (2ml) and the solution was stirred at the same temperature for 1-2 hr. After removing the solvent under reduced pressure, the residue was dissolved in toluene and solvent was again removed under reduced pressure. The latter operation was repeated to remove all the trifluoroacetic acid. The residue was dried (in vacuo) to obtain the trifluoroacetate salts of the respective dipeptides. Wherever possible, the trifluoroacetate salts were characterized from spectral data and physical constants recorded.

**Synthesis of Dap-Phe-$OCH_3$ Tfa (2a):**

After removing toluene under reduced pressure, the residue obtained as a thick oily mass was triturated with ether to obtain the trifluoroacetate salt (**2a**, quantitative) as a colorless crystalline solid: IR(thin film): 3275, 2928, 1744, 1674, 1541, 1456, 1202, 1132 and 721; $^1$H NMR (300MHz, $CDCl_3$): 1.107(brs, 3H, $CH_3$), 1.60-2.10(m, 4H, 2 x $CH_2$), 2.60(m, 1H, CHCO), 2.90-3.00(m, 2H, $CH_2$-Ph), 3.10-3.35(m, 3H, C<u>H</u>-$OCH_3$, $CH_2$-N), 3.209(s, 3H, $OCH_3$), 3.40-3.55(m, 1H, pro CH-N), 3.712(s, 3H, $COOCH_3$), 4.75(m, 1H, phe CH-N), 7.106(m, 1H, NH), 7.124-7.324(m, 5H, Ph) and 8.7(m, 1H, NH); HRFABMS: m/z 349.21350(100%, cation); $[C_{19}H_{29}N_2O_4]^+$ requires 349.21273.

**Synthesis of Dap-Phe-$NH_2$ Tfa (2b):**

Removal of toluene under reduced pressure left the trifluoroacetate salt (2b, 97% ) as a colorless solid.

**Synthesis of Dap-Pro-$OCH_3$ Tfa (2c):**

After removing toluene under reduced pressure, the residue obtained as a thick oily mass was triturated with ether to obtain the trifluoroacetate salt (2c, 99%) as a colorless crystalline solid: IR(thin film): 2980, 2890, 1746, 1680, 1626, 1437, 1287, 1200, 1094, 799 and 721; $^1H$ NMR (300MHz, $CDCl_3$): 1.307(d, J=6.9Hz, 3H, $CH_3$), 1.85-2.30(m, 8H, 4 x $CH_2$), 2.85(m, 1H, CH-CO), 3.20-3.40(m, 1H, CH-$OCH_3$), 3.485(s, 3H, $CH_3$), 3.35-3.75(m, 3H, CH-N, $CH_2$-N), 3.687(s, 3H, $COOOCH_3$), 4.165(m, 2H, $CH_2$-$N^+$), 4.442(m, 1H, CH-$N^+$) and 8.008(m, NH). HRFABMS: m/z 299.19770(100%, cation); $[C_{15}H_{27}N_2O_4]^+$ requires 299.1971.

**Synthesis of Dap-Ile-$OCH_3$ Tfa (2d):**

After removing toluene under reduced pressure, the residue obtained as a thick oily mass was triturated with ether to obtain the trifluoroacetate salt (2d, 97%) as a gummy mass: IR(thin film): 3289, 2969, 2884, 1744, 1674, 1541, 1458, 1383, 1202, 1136, 833, 799 and 721; $^1H$ NMR (300MHz, $CDCl_3$): 0.88(brs, 3H, $\underline{CH_3}$), 1.884(t, J=6.7Hz, 3H, $\underline{CH_3}$-$CH_2$), 1.209(d, J=6.8Hz, $\underline{CH_3}$-CH), 1.10-1.50(m, 2H, $CH_2$), 1.80-2.20(m, 5H, 2 X $CH_2$, $CH_3$-$\underline{CH}$), 2.707(m, 1H, CH-CO), 3.10-3.41(m, 2H, $CH_2$-N), 3.470(s, 3H, $OCH_3$), 3.60-3.70(M, 1H, $\underline{CH}$-$OCH_3$), 3.48-3.85-3.90(m, 1H, pro $\underline{CH}$-N), 3.702(s, 3H, $COOCH_3$), 4.43(dd, J=7.5 and 5.4Hz, 1H, ile CH-N), 6.926(d, J=7.9Hz, 1H, NH), 8.8(m, 1H, 1/2 $NH_2$) and 10(m, 1H, 1/2 $NH_2$); MS: HRFAB: m/z 315.22890(100%. Cation); $[C_{16}H_{31}N_2O_4]^+$ requires 315.22838.

**Synthesis of Dap-Met-$OCH_3$ Tfa (2e):**

Removal of toluene under reduced pressure left the trifluoroacetate salt (2e, quantitative) as a gummy mass.

**SYNTHESIS OF PENTAPEPTIDES 3a-e - GENERAL PROCEDURE:**

To a solution of the tripeptide tfa salt (4, 1mmol) and the dipeptide tfa salt (1mmol) in dichloromethane (2ml, ice-bath and under argon) was added dry triethylamine (3mmol) followed by diethylcyanophosphonate (1.1mmol). The solution was stirred at the same temperature for 1-2hr. After removing solvent under reduced pressure the residue was chromatographed on a SILICA GEL column using the solvent system given below as eluents to obtain the respective pentapeptides (3a-e).

**Dov-Val-Dil-Dap-Phe-$OCH_3$ (3a):**

Chromatographic separation on a SILICA GEL column with 3:4 hexane-acetone as the eluent gave the required pentapeptide(3a, 87%); m.p. = 80-83°C ; $[\alpha]_D^{25}$ = -35.3° (c 0.34, $CHCl_3$); IR(thin film): 3298, 2963, 2934, 2876, 2830, 2787, 1748, 1622, 1532, 1454, 1379, 1269, 1200, 1099, 1038, 737 and 700; MS: m/z 759($M^+$), 716, 481, 449, 433, 227, 186, 154, 128, 100(100%), 85 and 70. Anal. Found: C: 64.91, H: 9.33, N: 8.97. $C_{41}H_{69}N_5O_8$ requires C: 64.71, H: 9.15, N: 9.22.

**Dov-Val-Dil-Dap-Phe-$NH_2$ (3b):**

Chromatographic separation on a SILICA GEL column with 1:3 hexane-acetone as the eluent resulted in the required pentapeptide as colorless powder (3b, 99%); m.p. = 111-113°C ; $[\alpha]_D^{25}$ = -42° (c 0.25, $CHCl_3$); IR(thin film): 3304, 3138, 3054, 2965, 2934, 2876, 2830, 2787, 1622, 1541, 1499, 1423,

1371, 1306, 1252, 1202, 1171, 1098, 1038, 756, 735 and 696; MS: m/z 744($M^+$), 701, 669, 519, 481, 418, 227, 206, 186, 170, 154, 128 and 114.

**Dov-Val-Dil-Dap-Pro-$OCH_3$ (3c):**

Chromatographic purification using a SILICA GEL column with 1:3 hexane-acetone as the eluent yielded the required pentapeptide as colorless powder (3c, 69%); m.p. = 75-77°C ; $[\alpha]_D^{25}$ = -52.7° (c 0.11, $CHCl_3$); IR(thin film): 3293, 2963, 2876, 2830, 2789, 1750, 1624, 1422, 1385, 1273, 1198, 1096, 1040 and 733; MS: m/z 709($M^+$), 666, 581, 481, 449, 412, 383, 369, 297, 255, 227(100%), 199, 186, 170 and 155. Anal. Found: C: 62.51, H: 9.61, N: 9.72. $C_{37}H_{67}N_5O_8$ requires C: 62.59, H: 9.51, N: 9.87.

**Dov-Val-Dil-Dap-Ile-$OCH_3$ (3d):**

Chromatographic separation on a SILICA GEL column with 1:2 hexane-acetone as the eluent gave the required pentapeptide as colorless powder (3d, 80% ); m.p. = 80-82°C; $[\alpha]_D^{25}$ = -39.3° (c 0.14, $CHCl_3$); IR(thin film): 3300, 3050, 2965, 2878, 2830, 2787, 1746, 1622, 1530, 1454, 1383, 1267, 1120, 1099, 1038 and 735; MS: m/z 725($M^+$), 682, 481, 399, 227, 186, 170, 154 and 128. Anal. Found: C: 63.03, H: 10.01, N: 9.77. $C_{38}H_{71}N_5O_8$ requires C: 62.86, H: 9.86, N: 9.65.

**Dov-Val-Dil-Dap-Met-$OCH_3$ (3e):**

Chromatographic separation using a SILICA GEL column with 1:2 hexane-acetone as the eluent resulted in the required pentapeptide as colorless powder (3e, 78%); m.p. = 63-65°C; $[\alpha]_D^{25}$ = -44.1° (c, 0.44, $CHCl_3$); IR(thin film): 3297, 2963, 2934, 2876, 2830, 2787, 1750, 1620(br), 1539, 1449, 1420, 1375, 1198 and 1098; MS (m/z): 743 ($M^+$), 700, 611, 568, 481, 417, 311, 227 and 154. Anal. Found: C: 59.78, H: 9.14, N: 9.16, S: 4.39. $C_{37}H_{69}N_5O_{68}S$ requires C:

59.73, H: 9.35, N: 9.41, S: 4.31.

To further aid in the understanding of the present invention, and not by way of limitation, the following examples are presented.

**Example Ia - Synthesis of Boc-Dap-Phe-$OCH_3$ (1a):**

The general procedure for the synthesis of dipeptides (1a-1e) was followed. The numerical identificate shown in Scheme 1 is followed herein. Chromatographic separation on a SILICA GEL column with 3:1 hexane-acetone as the eluent resulted in the required dipeptide as a thick oil. Crystallization from ether-hexane gave sparkling crystals of the pure compound (**1a**, 96%); m.p. = 125°C; $[\alpha]_D^{25}$ = -15.1 (c 0.41, $CHCl_3$); IR(thin film): 3314, 2974, 2934, 2878, 1748, 1692, 1663, 1537, 1456, 1400, 1366, 1173, 1101 and 700; $^1H$ NMR (300MHz, $CDCl_3$): 1.163(d, J=7.0Hz, 3H, $CH_3$), 1.4816(s, 9H, t-Bu), 1.624-1.850(m, 4H, 2 x $CH_2$), 2.25-2.45(m, 1H, CHCO), 3.045(dd, J=13.9 and 7.8Hz, 1H, 1/2 $CH_2$-Ph), 3.175(dd, J=13.8 and 5.55Hz, 1H, 1/2 $CH_2$-Ph), 3.3642(s, 3H, $OCH_3$), 3.3701(s, 3H, $OCH_3$), 3.50-3.60(m, 1H, CH-$OCH_3$), 3.7422(m, 2H, $CH_2$-N), 3.85(m, 1H, pro CH-N), 4.80(m, 1H, phe CH-N), 6.10, 6.75(m, 1H, NH) and 7.10-7.32(m, 5H, Ph); MS: m/z 416(M-MeOH), 375, 316, 264, 210, 170, 114(100%) and 70. Anal. Found: H: 8.12, N: 6.20. $C_{24}H_{36}N_2O_6$ requires H: 8.09, N: 6.25.

**Example Ib - Synthesis of Boc-Dap-Phe-$NH_2$ (1b):**

The general procedure for the synthesis of dipeptides (1a-1e) was followed. Chromatographic purification using a SILICA GEL column with 1:1 hexane-acetone as the eluent gave the required dipeptide as a crystalline solid. Recrystallization from acetone gave sparkling crystals of the pure compound (**1b**, 65%); m.p. =

199-200°C (acetone); $[\alpha]_D^{25}$ = -40 (c 0.15, $CHCl_3$); IR(thin film): 3302, 3198, 2974, 2934, 2878, 1669, 1539, 1456, 1404, 1366, 1169, 1111 and 700; $^1H$ NMR (300MHz, $CDCl_3$): 1.019(brs, 3H, $CH_3$), 1.426(s, 9H, t-Bu), 1.55-1.90(m, 4H, 2 x $CH_2$), 2.30(quintet, 1H, CH-CO), 3.00-3.25(m, 3H, $CH_2$-N, CH-$OCH_3$), 3.349(s, 3H, $OCH_3$), 3.60-3.75(m, 1H, pro CH-N), 4.60-4.80(m, 1H, phe CH-N), 5.30(brs, 1H, NH), 6.287(d, J=7.2Hz, 1H, NH), 6.90(brm, 1H, NH) and 7.164-7.306(m, 5H, $C_6H_5$); MS: m/z 433($M^+$), 401(M-MeOH), 360, 301, 247, 232, 210, 170, 154, 138, 114 and 70(100%). Anal. Found: C: 63.75, H:8.18, N:9.62. $C_{23}H_{35}N_3O_5$ requires C: 63.72, H: 8.14, N: 9.69.

**Example Ic - Synthesis of Boc-Dap-Pro-$OCH_3$ (1c):**

The general procedure for the synthesis of dipeptides was followed. Chromatographic separation on a SILICA GEL column with 3:2 hexane-acetone as the eluent gave the required dipeptide as a thick oil (1c, 92%); $[\alpha]_D^{25}$ = -101.5 (c 0.2, $CHCl_3$); IR(neat): 2974, 2880, 1748, 1692, 1647, 1398, 1366, 1171and 1098; $^1H$ NMR (300MHz, $CDCl_3$): 1.222(d, J=7.0Hz, 3H, $CH_3$), 1.440(s, 9H, t-Bu), 1.65-2.20(m, 8H, 4 x $CH_2$), 2.60-2.70(m, 1H, CH-CO), 3.10-3.22(m, 1H, CH-$OCH_3$), 3.417(s, 3H, $CH_3$), 3.45-3.65(m, 4H, 2 x $CH_2$-N), 3.675(s, 3H, $OCH_3$), 3.74-3.83(m, 1H, CH-N) and 4.447(dd, J=8.55 and 3.5Hz, 1H, CH-$COOCH_3$). HRFABMS: m/z 399.24880$(M+H)^+$;. $[C_{20}H_{35}N_2O_6]^+$ requires 399.24951.

**Example Id - Synthesis of Boc-Dap-Ile-$OCH_3$ (1d):**

The general procedure for the synthesis of dipeptides (1a-1e) was followed. Chromatographic purification on a SILICA GEL column with 3:2 hexane-ethyl acetate as the eluent yielded the required dipeptide as an oily liquid (1d, 72%); m.p. = 76-77°C (acetone); $[\alpha]_D^{25}$ = -28.2 (c 0.17, $CHCl_3$); IR(thin film): 3325, 2971, 2936, 2878, 1746, 1694, 1667, 1530, 1478, 1398, 1254, 1175, 1105, 868

and 774; $^1$H NMR (300MHz, $CDCl_3$): 0.882(d, J=6.9Hz, 3H, $\underline{CH_3}$-CH), 0.9012(t, J=7.4Hz, 3H, $\underline{CH_3}$-$CH_2$), 1.05-1.24(m, 5H, $CH_3$, $\underline{CH_2}$-$CH_3$), 1.4526(s, 9H, t-Bu), 1.65-2.00(m, 5H, 2 x $CH_2$, $\underline{CH}$-$CH_2$), 2.30-2.50(m, 1H, CH-CO), 3.18-3.28(m, 1H, $\underline{CH}$-$OCH_3$), 3.422(s, 3H, $OCH_3$), 3.48-3.60(m, 1H, pro $\underline{CH}$-N), 3.699(s, 3H, $OCH_3$), 3.72-3.82(m, 1H, 1/2 $CH_2$-N), 3.88-3.98(m, 1H, 1/2 $CH_2$-N), 4.44-4.58(m, 1H, ile CH-N) and 6.15, 6.7(m, 1H, NH); MS: m/z 382(M-MeOH), 341, 282, 245, 230, 210, 170, 114, 70(100%) and 57. Anal. Found: C: 61.06, H: 9.25, N: 6.64. $C_{21}H_{38}N_2O_6$ requires C: 60.84, H: 9.24, N: 6.76.

**Example Ie - Synthesis of Boc-Dap-Met-$OCH_3$ (1e):**

The general procedure for the synthesis of dipeptides (1a-1e) was followed. Chromatographic separation on a SILICA GEL column using 3:2 hexane-acetone as the eluent gave the required dipeptide as a solid (1e, 83%); m.p. = 68-70°C; $[\alpha]_D^{25}$= -27.6 (c, 0.59, $CHCl_3$); IR(neat): 3312, 2974, 2934, 2878, 1748, 1692, 1663, 1539, 1398, 1366, 1256, 1171, 1115, 866 and 774; $^1$H NMR ($CDCl_3$): 1.223(brs, 3H, CH-$CH_3$), 1.441(brs, 9H, t-Bu), 1.6-1.2(m, 6H, 3x$CH_2$), 2.070 (s, 3H, S-$CH_3$), 2.3-2.55(m, 3H, $CH_2$-S, CH-CO), 3.15-3.35 (m, 2H, N-$CH_2$), 3.420 (s, 3H, $OCH_3$), 3.55(m, 1H, CH-$OCH_3$), 3.716(brs, 3H, $COOCH_3$), 3.85-4.0(m, 1H, pro CH-N), 4.6(brm, 1H, met CH-N), 6.3(brm, 1H, NH); MS (m/z): 432 ($M^+$), 400, 359, 258, 210, 170, 114(100%). Anal. Found: C: 55.35, H: 8.33, N: 6.53, S: 7.23. $C_{20}H_{36}N_2O_6$ S requires C: 55.53, H: 8.39, N: 6.48, S: 7.41.

**Example IIa - Synthesis of Dap-Phe-$OCH_3$ Tfa (2a):**

General procedure A was followed. After removing toluene under reduced pressure, the residue obtained as a thick oily mass was titrated with ether to obtain the trifluoroacetate salt (2a, quantitative) as a colorless crystalline solid: IR(thin film): 3275, 2928, 1744, 1674, 1541, 1456,

1202, 1132 and 721; $^1$H NMR (300MHz, $CDCl_3$): 1.107(brs, 3H, $CH_3$), 1.60-2.10(m, 4H, 2 x $CH_2$), 2.60(m, 1H, CHCO), 2.90-3.00(m, 2H, $CH_2$-Ph), 3.10-3.35(m, 3H, C<u>H</u>-$OCH_3$, $CH_2$-N), 3.209(s, 3H, $OCH_3$), 3.40-3.55(m, 1H, pro CH-N), 3.712(s, 3H, $COOCH_3$), 4.75(m, 1H, phe CH-N), 7.106(m, 1H, NH), 7.124-7.324(m, 5H, Ph) and 8.7(m, 1H, NH); HRFABMS: m/z 349.21350(100%, cation); $[C_{19}H_{29}N_2O_4]^+$ requires 349.21273.

**Example IIb - Synthesis of Dap-Phe-$NH_2$ Tfa (2b):**

General procedure A was followed. Removal of toluene under reduced pressure left the trifluoroacetate salt (2b, 97%) as a colorless solid.

**Example IIc - Synthesis of Dap-Pro-$OCH_3$ Tfa (2c):**

General procedure A was followed. After removing toluene under reduced pressure, residue obtained as a thick oily mass was triturated with ether to obtain the trifluoroacetate salt (2c, 99%) as a colorless crystalline solid: IR(thin film): 2980, 2890, 1746, 1680, 1626, 1437, 1287, 1200, 1094, 799 and 721; $^1$H NMR (300MHz, $CDCl_3$): 1.307(d, J=6.9Hz, 3H, $CH_3$), 1.85-2.30(m, 8H, 4 x $CH_2$), 2.85(m, 1H, CH-CO), 3.20-3.40(m, 1H, CH-$OCH_3$), 3.485(s, 3H, $CH_3$), 3.35-3.75(m, 3H, CH-N, $CH_2$-N), 3.687(s, 3H, $COOOCH_3$), 4.165(m, 2H, $CH_2$-$N^+$), 4.442(m, 1H, CH-$N^+$) and 8.008(m, NH). HRFABMS: m/z 299.19770(100%, cation); $[C_{15}H_{27}N_2O_4]^+$ requires 299.1971.

**Example IId - Synthesis of Dap-Ile-$OCH_3$ Tfa (2d):**

General procedure A was followed. After removing toluene under reduced pressure, the residue obtained as a thick oily mass was triturated with ether to obtain the trifluoroacetate salt (2d, 97%) as a gummy mass: IR(thin film): 3289, 2969, 2884, 1744, 1674, 1541, 1458, 1383, 1202, 1136, 833, 799 and 721; $^1$H NMR (300MHz,

$CDCl_3$): 0.88(brs, 3H, $\underline{CH_3}$), 1.884(t, J=6.7Hz, 3H, $\underline{CH_3}$-$CH_2$), 1.209(d, J=6.8Hz, $\underline{CH_3}$-CH), 1.10-1.50(m, 2H, $CH_2$), 1.80-2.20(m, 5H, 2 X $CH_2$, $CH_3$-$\underline{CH}$), 2.707(m, 1H, CH-CO), 3.10-3.41(m, 2H, $CH_2$-N), 3.470(s, 3H, $OCH_3$), 3.60-3.70(M, 1H, $C\underline{H}$-$OCH_3$), 3.85-3.90(m, 1H, pro $\underline{CH}$-N), 3.702(s, 3H, $COOCH_3$), 4.43(dd, J=7.5 and 5.4Hz, 1H, ile CH-N), 6.926(d, J=7.9Hz, 1H, NH), 8.8(m, 1H, 1/2 $NH_2$) and 10(m, 1H, 1/2 $NH_2$); MS: HRFAB: m/z 315.22890(100%. cation); $[C_{16}H_{31}N_2O_4]^+$ requires 315.22838.

**Example IIe - Synthesis of Dap-Met-$OCH_3$ Tfa (2e):**

General procedure A was followed. Removal of toluene under reduced pressure left the trifluoroacetate salt (**2e**, quantitative) as a gummy mass.

**Example IIIa - Synthesis of Dov-Val-Dil-Dap-Phe-$OCH_3$ (3a):**

Chromatographic separation on a SILICA GEL column with 3:4 hexane-acetone as the eluent gave the required pentapeptide(**3a**, 87%); m.p. = 80-83°C ; $[\alpha]_D^{25}$= -35.3 (c 0.34, $CHCl_3$); IR(thin film): 3298, 2963, 2934, 2876, 2830, 2787, 1748, 1622, 1532, 1454, 1379, 1269, 1200, 1099, 1038, 737 and 700; MS: m/z 759($M^+$), 716, 481, 449, 433, 227, 186, 154, 128, 100(100%), 85 and 70. Anal. Found: C: 64.91, H: 9.33, N: 8.97. $C_{41}H_{69}N_5O_8$ requires C: 64.71, H: 9.15, N: 9.22.

**Example IIIb - Synthesis of Dov-Val-Dil-Dap-Phe-$NH_2$ (3b):**

General procedure B was followed. Chromatographic separation on a SILICA GEL column with 1:3 hexane-acetone as the eluent resulted in the required pentapeptide as colorless powder (**3b**, 99%); m.p. = 111-113°C ; $[\alpha]_D^{25}$= -42 (c 0.25, $CHCl_3$); IR(thin film): 3304, 3138, 3054, 2965, 2934, 2876, 2830, 2787, 1622, 1541, 1499, 1423, 1371, 1306,

1252, 1202, 1171, 1098, 1038, 756, 735 and 696; MS: m/z 744($M^+$), 701, 669, 519, 481, 418, 227, 206, 186, 170, 154, 128 and 114.

**Example IIIc - Synthesis of Dov-Val-Dil-Dap-Pro-$OCH_3$ (3c):**

General procedure B was followed. Chromatographic purification using a SILICA GEL column with 1:3 hexane-acetone as the eluent yielded the required pentapeptide as colorless powder (3c, 69%); m.p. = 75-77°C ; $[\alpha]_D^{25}$= -52.7 (c 0.11, $CHCl_3$); IR(thin film): 3293, 2963, 2876, 2830, 2789, 1750, 1624, 1422, 1385, 1273, 1198, 1096, 1040 and 733; MS: m/z 709($M^+$), 666, 581, 481, 449, 412, 383, 369, 297, 255, 227(100%), 199, 186, 170 and 155. Anal. Found: C: 62.51, H: 9.61, N: 9.72. $C_{37}H_{67}N_5O_8$ requires C: 62.59, H: 9.51, N: 9.87.

**Example IIId - Synthesis of Dov-Val-Dil-Dap-Ile-$OCH_3$ (3d):**

General procedure B was followed. Chromatographic separation on a SILICA GEL column with 1:2 hexane-acetone as the eluent gave the required pentapeptide as colorless powder (3d, 80%); m.p. = 80-82°C ; $[\alpha]_D^{25}$= -39.3 (c 0.14, $CHCl_3$); IR(thin film): 3300, 3050, 2965, 2878, 2830, 2787, 1746, 1622, 1530, 1454, 1383, 1267, 1120, 1099, 1038 and 735; MS: m/z 725($M^+$), 682, 481, 399, 227, 186, 170, 154 and 128. Anal. Found: C: 63.03, H: 10.01, N: 9.77. $C_{38}H_{71}N_5O_8$ requires C: 62.86, H: 9.86, N: 9.65.

**Example IIIe - Synthesis of Dov-Val-Dil-Dap-Met-$OCH_3$ (3e):**

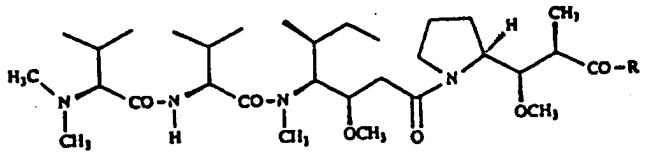
General procedure B was followed. Chromatographic separation using a SILICA GEL column with 1:2 hexane-acetone as the eluent resulted in the required pentapeptide as colorless

powder (3e, 78%); m.p. = 63-65°C; $[\alpha]_D^{25}$= -44.1 (c, 0.44, $CHCl_3$); IR(thin film): 3297, 2963, 2934, 2876, 2830, 2787, 1750, 1620(br), 1539, 1449, 1420, 1375, 1198 and 1098; MS (m/z): 743 ($M^+$), 700, 611, 568, 481, 417, 311, 227 and 154. Anal. Found: C: 59.78, H: 9.14, N: 9.16, S: 4.39. $C_{37}H_{69}N_5O_{68}S$ requires C: 59.73, H: 9.35, N: 9.41, S: 4.31.

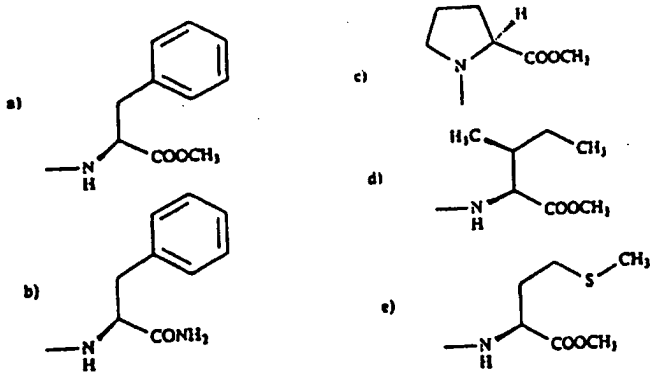
From the foregoing, it is readily apparent that a useful embodiment of the present invention has been herein described and illustrated which fulfills all of the aforestated objectives in a remarkably unexpected fashion. It is of course understood that such modifications, alterations and adaptations as may readily occur to the artisan confronted with this disclosure are intended within the spirit of this disclosure which is limited only by the scope of the claims appended hereto.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A compound having the structural formula designated **3(a-e)**:



wherein R is selected from the following group of substituents:




2. A compound according to claim 1 in which R is the substituent designated a.

3. A compound according to claim 1 in which R is the substituent designated b.

4. A compound according to claim 1 in which R is the substituent designated c.

5. A compound according to claim 1 in which R is the substituent designated d.

6. A compound according to claim 1 in which R is the substituent designated e.

7. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound as defined in any one of claims 1 to 6, and a pharmaceutically acceptable carrier.

8. Use of a compound as defined in any one of claims 1 to 6, for inhibiting the growth of human cancer cells responsive thereto.

9. A method of synthesizing a pentapeptide as defined in claim 1, which comprises: selecting dolaproine tfa salt; selecting an amino acid salt; dissolving said amino acid salt in cooled dry dichloromethane and triethylamine; adding said dolaproine tfa salt to said amino acid salt solution to produce a solution; adding diethylcyano-phosphonate (DECP) to said solution; cooling said DECP-containing solution to cause precipitation in the solution; evaporating the solvents from said precipitate-containing solution under reduced pressure to leave a residue; chromatographing said residue over a SILICA GEL column with solvents to isolate the respective dipeptide; dissolving said dipeptide in cooled dry dichloromethane and adding trifluoroacetic acid thereto to create a second solution; stirring said second solution, removing solvent from said second solution, under reduced pressure to provide a second residue; repeatedly dissolving said second residue in toluene and thereafter evaporating said solvent therefrom to remove all trifluoroacetic acid from said second residue; drying said second residue in vacuo thereby to obtain the trifluoroacetate salt of the respective dipeptide; admixing the respective tripeptide tfa salt to said dipeptide salt; dissolving said salts in dichloromethane in an ice-bath under an argon atmosphere to form a third solution; adding dry triethylamine to said third solution and

thereafter; adding diethylcyanopho- phonate thereto to form a resultant fourth solution; stirring said fourth solution; removing solvent from said fourth solution under reduced pressure to leave a third residue; and chromatographing said third residue on a SILICA GEL column to isolate the desired pentapeptide.

10. An in vitro method for inhibiting the growth of human cancer cells in an environment which comprise administering a pharmaceutically acceptable carrier combined with an amount of an active agent which is selected from the compounds claimed in any one of claims 1 to 6 effective to inhibit the growth and effects of tumor cells in human cancer cells within the environment to which the administration is effected.

11. An in vitro method for inhibiting the growth of human cancer cells wherein said cancer is selected from the group consisting of leukemia, ovarian cancer, CNS cancer, mammary cancer, non-small cell lung cancer, renal cancer, colon cancer, and melanoma consisting of administering an active ingredient selected from the group consisting of: Dov-Val-Dil-Dap-Phe-$OCH_3$, Dov-Val-Dil-Dap-Phe-$NH_2$, Dov-Val-Dil-Dap-Pro-$OCH_3$, Dov-Val-Dil-Dap-Ile-$OCH_3$, and Dov-Val-Dil-Dap-Met-$OCH_3$, to said cells in a quantity sufficient to inhibit the growth of said cells.

12. An in vitro method according to claim 11 wherein said active ingredient consists of Dov-Val-Dil-Dap-Phe-$OCH_3$.

13. An in vitro method according to claim 11 wherein said active ingredient consists of Dov-Val-Dil-Dap-Phe-$NH_2$.

14. An in vitro method according to claim 11 wherein said active ingredient consists of Dov-Val-Dil-Dap-Pro-$OCH_3$.

15. An in vitro method according to claim 11 wherein said active ingredient consists of Dov-Val-Dil-Dap-Ile-$OCH_3$.

16. An in vitro method according to claim 11 wherein said active ingredient consists of Dov-Val-Dil-Dap-Met-$OCH_3$.

17. An in vitro method according to claim 11 for inhibiting the growth of human cancer cells selected from the group of cell lines consisting of P388 Lymphotic Leukemia, L1210 Lumphatic Leukemia, B16 Melanoma, M5076 Ovary Sarcoma, LOX Human Melanoma, Human Mammary MX-7, and OVCAR-3, consisting of administering an active ingredient selected from the group consisting of Dov-Val-Dil-Dap-Phe-$OCH_3$, Dov-Val-Dil-Dap-Phe-$NH_2$, Dov-Val-Dil-Dap-Pro-$OCH_3$, Dov-Val-Dil-Dap-Ile-$OCH_3$, and Dov-Val-Dil-Dap-Met-$OCH_3$, to said cells in a quantity sufficient to inhibit the growth of said cells.

18. An in vitro method according to claim 11 wherein said cancer is selected from the group of cell lines consisting of P388, OVCAR-3, SF-295, A498, NCI-H460, KM20L2, and SK-MEL-3.

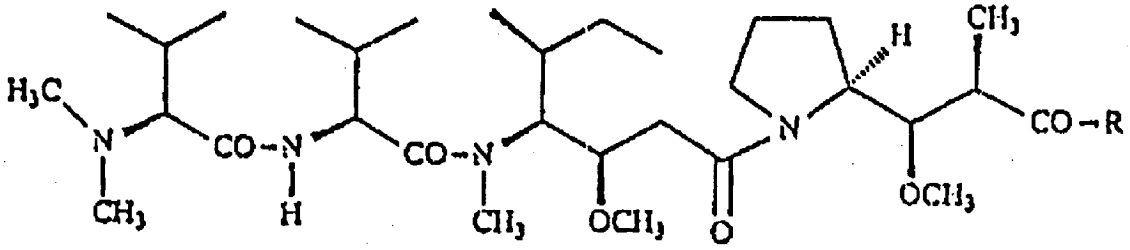
19. An in vitro method according to claim 18 wherein said active ingredient consists of Dov-Val-Dil-Dap-Phe-$OCH_3$.

20. An in vitro method according to claim 18 wherein said active ingredient consists of Dov-Val-Dil-Dap-Phe-$NH_2$.

21. An in vitro method according to claim 18 wherein said active ingredient consists of Dov-Val-Dil-Dap-Pro-$OCH_3$.

22. An in vitro method according to claim 18 wherein said active ingredient consists of Dov-Val-Dil-Dap-Ile-$OCH_3$.

23. An in vitro method according to claim 18 wherein said active ingredient consists of Dov-Val-Dil-Dap-Met-$OCH_3$.



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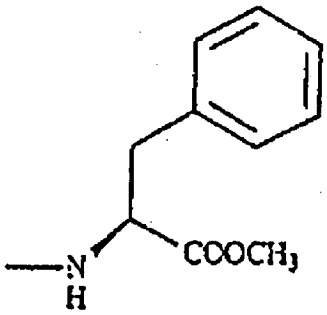
a)



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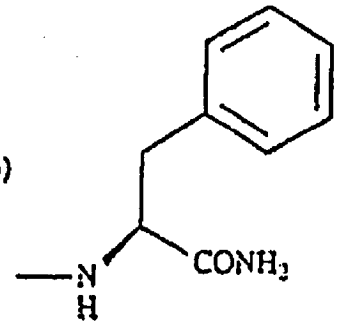

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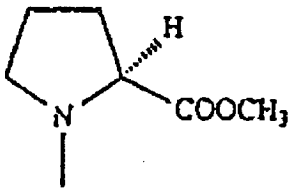

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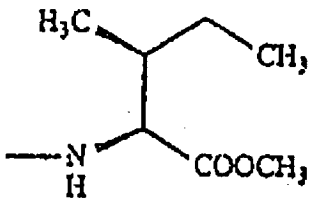

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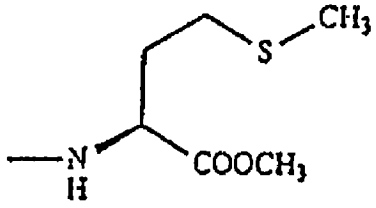

(II)